

Supplementary Appendix

Supplement to: Li BT, Smit EF, Goto Y, et al. Trastuzumab deruxtecan in *HER2*-mutant non–small-cell lung cancer. *N Engl J Med* 2022;386:241-51. DOI: 10.1056/NEJMoa2112431

This appendix has been provided by the authors to give readers additional information about the work.

SUPPLEMENTARY APPENDIX

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List of Investigators

Country, Study Site	Principal Investigator
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Kindai University Hospital	Kazuhiko Nakagawa

Additional Data Sharing Information

Data Sharing Questions	Answers
Will individual participant data be available (including data dictionaries)?	Yes
What data in particular will be shared?	<p>Anonymized individual participant data (IPD) and applicable supporting clinical trial documents may be available upon request at (https://vivli.org). In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo Companies will continue to protect the privacy of the company and our clinical study subjects. Details on data sharing criteria and the procedure for requesting access can be found at this web address:</p> <p>https://vivli.org/ourmember/daiichi-sankyo</p>
What other documents will be available?	<p>Clinical Trial Protocol, Statistical Analysis Plan, Informed Consent Form, and Clinical Study Report.</p> <p>In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo will continue to protect the privacy of our clinical trial participants.</p>
When will data be available (start and end dates)?	Anonymized IPD will be available when the indication supported receives marketing approval and study results are published.
With whom?	Qualified science and medical researchers upon formal request and submission of research proposal detailing planned analyses.

For what types of analyses?	Anonymized IPD and relevant clinical trial documents will be shared for the purpose of conducting legitimate research as specified in an approved formal research proposal.
By what mechanism will data be made available?	Anonymized IPD may be available upon request at https://vivli.org/

Supplementary Methods

Inclusion and Exclusion Criteria

Patients were excluded from the study if they had a history of myocardial infarction within 6 months before enrollment, symptomatic congestive heart failure 28 days before enrollment, unstable angina, or serious cardiac arrhythmia. Patients were also ineligible if they had clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses including, any underlying pulmonary disorder, and any autoimmune, connective tissue, or inflammatory disorders with potential pulmonary involvement, or prior pneumonectomy.

End Points

The following efficacy end points were analyzed in the study, not all of which are reported in the article. The primary efficacy end point was objective response rate. Secondary efficacy end points included duration of response, disease control rate, progression-free survival, and overall survival. Exploratory efficacy end points included time to response, best percent change in the sum of diameters for all target lesions, and potential biomarkers of response.

Along with the standard summary of safety end points (such as adverse events), clinical laboratory evaluations (hematology, biochemistry), electrocardiogram, vital signs, time to first onset of interstitial lung disease, and duration of first interstitial lung disease were also analyzed.

Safety

Safety parameters included the incidence of treatment-emergent adverse events and serious adverse events. Treatment-emergent adverse events were defined as adverse events that occurred or worsened in severity after initiating the study drug until 47 days after the last dose of the study drug. Serious adverse events with an onset or worsening ≥ 48 days after the last dose of the study drug, if considered related to the study treatment, were also considered treatment-emergent and were recorded.

For ongoing adverse events in the database, stop date is censored/imputed with the earliest among the date of death, date of start of new anticancer therapy, date of last study treatment + 47 days, or last contact date.

Subgroup Analysis

Several subgroup analyses (where the subgroups are defined by demographic and baseline characteristics of interest) for objective response rate, duration of response, progression-free survival (all based on independent central review), and overall survival were performed for the full analysis set.

Interstitial Lung Disease

An international, independent, multidisciplinary adjudication committee was responsible for reviewing all cases of potential interstitial lung disease/pneumonitis. Any reported cases of interstitial lung disease were identified for adjudication based on the current Medical Dictionary for Regulatory Activities (MedDRA) version for the narrow interstitial lung disease Standardized MedDRA Query (SMQ), selected terms from the broad interstitial lung disease SMQ, and the two preferred terms, respiratory failure and acute respiratory failure. Interstitial lung disease/pneumonitis was managed in accordance with the study protocol (**Table S2**).

Statistical Analysis

The 2-sided 95% confidence interval (CI)s were based on the exact (Clopper-Pearson) binomial distribution. The Kaplan-Meier method was used to estimate quartile event times for duration of response, progression-free survival, and overall survival. The 2-sided CIs of quartile event times were calculated using Brookmeyer and Crowley methods. Safety analyses were descriptive and reported with appropriate summary statistics.

Contributors

Bob T. Li, Egbert F. Smit, Julien Mazières, David Planchard, Pasi A. Jänne, Kapil Saxena, Ryota Shiga, Yingkai Cheng, Suddhasatta Acharyya, Patrik Vitazka, and Javad Shahidi contributed to the conception and/or design of the study and the development of the study protocol. Bob T. Li, Egbert F. Smit, Yasushi Goto, Kazuhiko Nakagawa, Hibiki Udagawa, Julien Manières, Misako Nagasaka, Lyudmila Bazhenova, Andreas N. Saltos, Enriqueta Felip, Jose M. Pacheco, Maurice Pérol, Luis Paz-Ares, David Planchard, and Pasi A. Jänne were involved in data collection. Suddhasatta Acharyya performed the data analysis. Patrik Vitazka performed the biomarker assessment. All authors participated in the interpretation of data. All authors were involved in the drafting and revision of the manuscript, and all authors approved the final version of the manuscript for publication.

Supplementary Figures and Tables

Figure S1. Trial Profile.

HER2, human epidermal growth factor receptor 2.

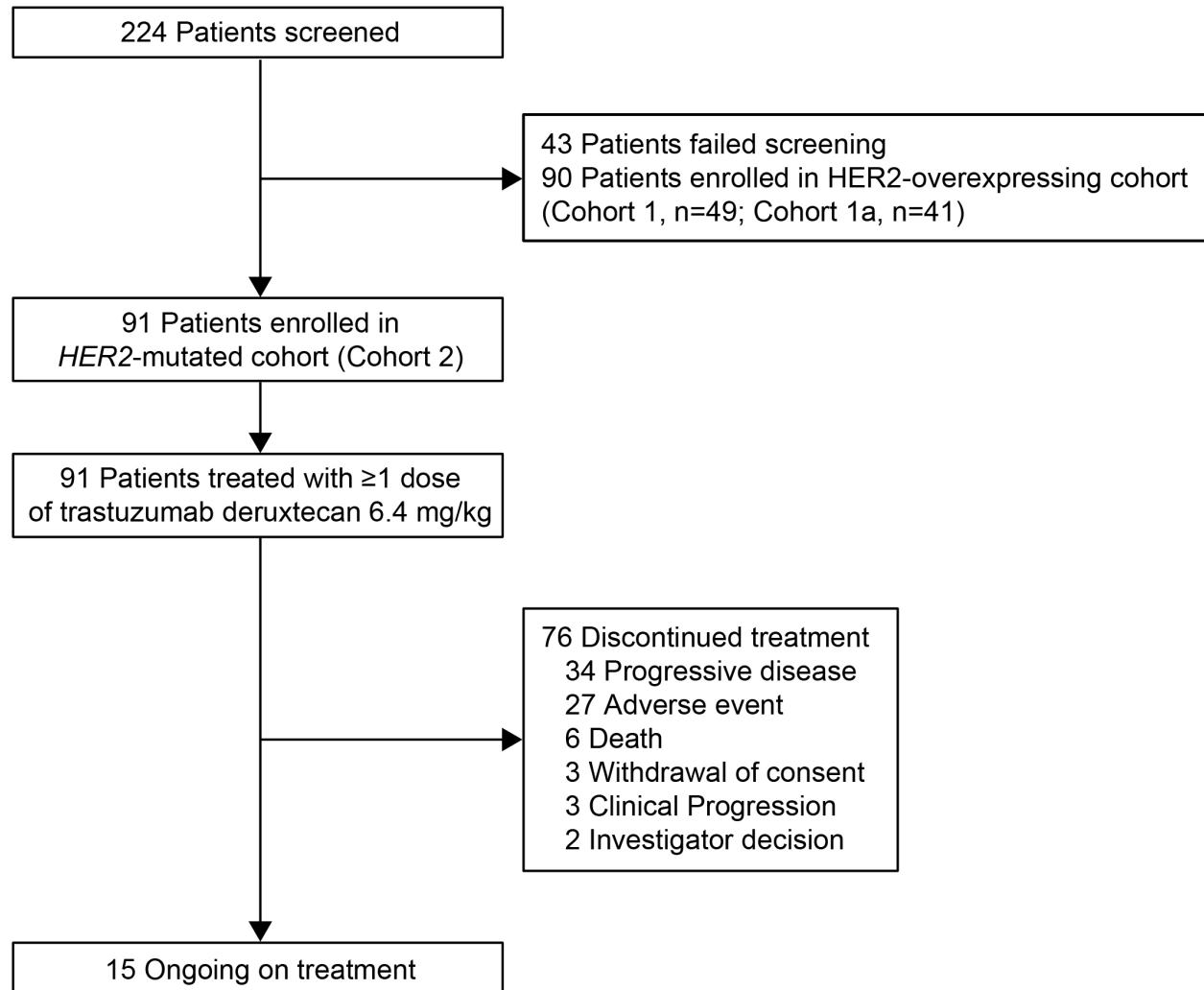


Figure S2. Response to Trastuzumab Deruxtecan.

CI, confidence interval; HER2, human epidermal growth factor receptor 2; PD-1, programmed death 1; PD-L1, programmed death ligand 1.

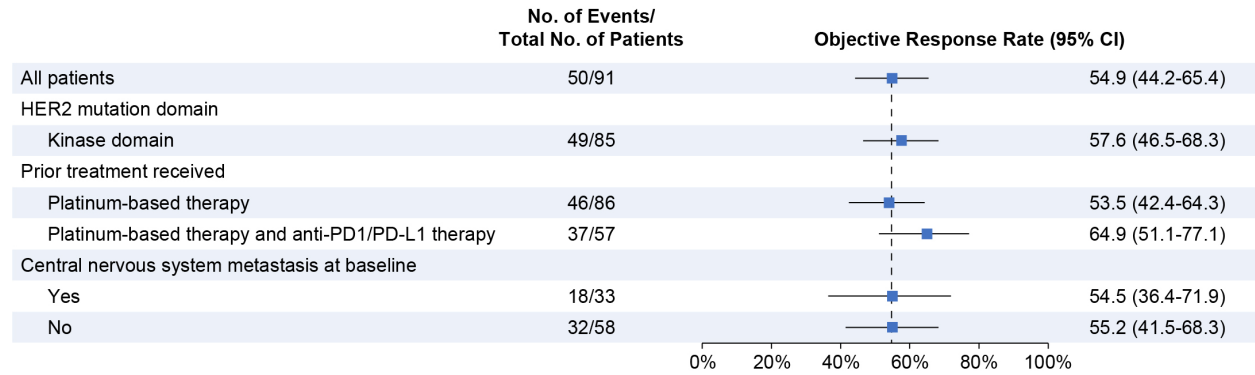


Table S1. List of Eligible *HER2* Mutations.*

<i>HER2</i> Mutations	Exon location	Domain location
Glu770 Ala771insAlaTyrValMet	20	Kinase
Ala771 Tyr772insTyrValMetAla	20	Kinase
Gly776delinsLeuCys	20	Kinase
Gly776Ser	20	Kinase
Gly776Cys	20	Kinase
Gly776delinsValCys	20	Kinase
Gly776Val	20	Kinase
Gly776Val777insLeu	20	Kinase
Val777Leu	20	Kinase
Val777Met	20	Kinase
Val777 Gly778insCysGly	20	Kinase
Gly778 Ser779insLeuProSer	20	Kinase
Val777 Gly778insGly	20	Kinase
Gly776 Val777insValGlySer	20	Kinase
Val777 Gly778insGlySerPro	20	Kinase
Ser310Pro	8	Extracellular
Ser310Tyr	8	Extracellular
Ser310Phe	8	Extracellular
Arg678Gln	17	Juxtamembrane
Thr733Ile	18	Kinase
Leu755Met	19	Kinase
Leu755Pro	19	Kinase
Leu755Ser	19	Kinase

<i>HER2</i> Mutations	Exon location	Domain location
Leu755Trp	19	Kinase
Asp769Asn	19	Kinase
Asp769His	19	Kinase
Asp769Tyr	19	Kinase

* In the earlier versions of protocol, any of the known activating *HER2* mutation was eligible with approval by the investigators and the sponsor. One patient with Ala775_Gly776insThrValMetAla was enrolled outside of the list.
HER2, human epidermal growth factor receptor 2.

Table S2. Management Guidelines for Pulmonary Toxicity.

CTCAE v5.0 Grade	Management Guidelines for Trastuzumab Deruxtecan*
	<p>If a subject develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever, rule out ILD/pneumonitis.</p> <p>If the AE is confirmed to have an etiology other than ILD/pneumonitis, follow the management guidance outlined in the “Other Non-Laboratory Adverse Events” in the dose modification section of the study protocol.</p> <p>If the AE is suspected to be ILD/pneumonitis, treatment with study drug should be interrupted pending further evaluation.</p> <p>Evaluations should include:</p> <ul style="list-style-type: none"> • High resolution CT • Pulmonologist consultation (Infectious Disease consultation as clinically indicated) • Blood culture and complete blood count (CBC). Other blood tests could be considered as needed • Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible • Pulmonary function tests and pulse oximetry (SpO₂) • Arterial blood gases if clinically indicated • One blood sample collection for PK analyses as soon as ILD/pneumonitis is suspected, if feasible • Other tests could be considered, as needed <p>If the AE is confirmed to be ILD/pneumonitis, follow the ILD/pneumonitis</p>

	<p>management guidance as outlined below.</p> <p>All events of ILD/pneumonitis regardless of severity or seriousness will be followed until resolution including after drug discontinuation.</p>
Grade 1	<p>The administration of trastuzumab deruxtecan must be interrupted for any ILD/pneumonitis events regardless of grade.</p> <ul style="list-style-type: none"> • Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks (or as clinically indicated) • Consider starting systemic glucocorticoids (eg, at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks • If worsening of diagnostic observations despite initiation of glucocorticoids, then follow Grade 2 guidelines* <p>For Grade 1 events, trastuzumab deruxtecan can be restarted only if the event is fully resolved to Grade 0:</p> <ul style="list-style-type: none"> • If resolved in ≤ 28 d from day of onset, maintain dose • If resolved in > 28 d from day of onset, reduce dose 1 level <p>However, if the event of Grade 1 ILD/pneumonitis occurs beyond Day 22 and has not resolved within 49 days from the last infusion, the study drug should be discontinued.</p> <p>*If subject is asymptomatic, then subject should still be considered as Grade 1 even if glucocorticoids were given</p>
Grade 2	<p>Permanently discontinue subject from study treatment.</p> <ul style="list-style-type: none"> • Promptly start and treat with systemic glucocorticoids (eg, at least 1mg/kg/day

	<p>prednisone or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks</p> <ul style="list-style-type: none"> • Monitor symptoms closely • Re-image as clinically indicated • If worsening or no improvement in clinical or diagnostic observations in 5 days: <ul style="list-style-type: none"> - Consider increasing dose of glucocorticoids (eg, 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (eg, methylprednisolone) - Reconsider additional work-up for alternative etiologies as described above - Escalate care as clinically indicated
Grade 3 and 4	<p>Permanently discontinue subject from study treatment.</p> <ul style="list-style-type: none"> • Hospitalization required • Promptly initiate empiric high-dose methylprednisolone IV treatment (eg, 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, then followed by a gradual taper over at least 4 weeks • Re-image as clinically indicated • If still no improvement within 3 to 5 days: <ul style="list-style-type: none"> - Reconsider additional work-up for alternative etiologies as described above - Consider other immuno-suppressants and/or treat per local practice

* These guidelines were updated in December 2019 during the course of the trial.

AE, adverse event; CT, computed tomography; CTCAE v5.0, Common Terminology Criteria for Adverse Events version 5.0; ILD, interstitial lung disease; IV, intravenous; PK, pharmacokinetics.

Table S3. Overall Safety Summary.

Type of adverse events — no. (%)	Patients (N = 91)
Any adverse event	91 (100)
Drug-related	88 (96.7)
Adverse event grade 3 or higher	63 (69.2)
Drug-related	42 (46.2)
Serious adverse event	39 (42.9)
Drug-related	18 (19.8)
Adverse event associated with discontinuation	34 (37.4)
Drug-related	23 (25.3)
Adverse event associated with dose reduction	32 (35.2)
Drug-related	31 (34.1)
Adverse event associated with dose interruption	44 (48.4)
Drug-related	29 (31.9)
Adverse event associated with an outcome of death	13 (14.3)
Drug-related	2 (2.2) ^a

^aOne patient experienced grade 3 interstitial lung disease as reported by investigator and died. The reported interstitial lung disease was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee.

Table S4. Most Common Adverse Events Reported by Investigators.

Incidence — no. (%)	Patients (N = 91)				
	Grade 1-2	Grade 3	Grade 4	Grade 5	All Grades
Patients with ≥1 adverse event	28 (30.8)	46 (50.5)	4 (4.4)	13 (14.3)	91 (100)
Adverse events with ≥20% incidence in all patients					
Nausea	61 (67.1)	8 (8.8)	0	0	69 (75.8)
Fatigue*	49 (53.9)	6 (6.6)	0	0	55 (60.4)
Vomiting	37 (40.7)	5 (5.5)	0	0	42 (46.2)
Alopecia	42 (46.2)	0	0	0	42 (46.2)
Diarrhea	34 (37.4)	2 (2.2)	1 (1.1)	0	37 (40.7)
Constipation	34 (37.4)	0	0	0	34 (37.4)
Anemia†	23 (25.3)	10 (11.0)	0	0	33 (36.3)
Decreased appetite	32 (35.2)	0	0	0	32 (35.2)
Neutropenia‡	15 (16.5)	14 (15.4)	3 (3.3)	0	32 (35.2)
Leukopenia§	17 (18.7)	4 (4.4)	0	0	21 (23.1)
Weight decreased	19 (20.9)	2 (2.2)	0	0	21 (23.1)
Pneumonitis	14 (15.4)	4 (4.4)	0	1 (1.1)	19 (20.9)

* This category includes fatigue, asthenia, and malaise.

† This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased.

‡ This category includes the preferred terms neutrophil count decreased and neutropenia.

§ This category includes the preferred terms white blood cell count decrease and leukopenia.

Table S5. Adjudicated Drug-related Interstitial Lung Disease.

	Patients (N = 91)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Adjudicated drug-related interstitial lung disease, n (%) [*]	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2) [†]	24 (26.4)

^{*} In some patients, glucocorticoids were not fully in line with the interstitial lung disease management guidelines.

[†] One patient with grade 5 interstitial lung disease had a history of partial lobectomy and 2 lines of prior cancer therapy, including 6 months of treatment with durvalumab immediately before starting the study drug. The patient was initially diagnosed with grade 3 pneumonitis 85 days after the first infusion of trastuzumab deruxtecan. Three days later, the patient received oral prednisone 1.5 mg per kilogram daily for 8 days, followed by intravenous methylprednisolone 500 mg daily for 4 days. The patient died 18 days later after the event onset. The other patient with grade 5 interstitial lung disease had a history of lobectomy and 1 line of prior cancer therapy, including 2 months of treatment with pembrolizumab immediately before starting the study drug. The patient was initially diagnosed with grade 3 interstitial lung disease 114 days after the first infusion of trastuzumab deruxtecan. Five days later, the patient received intravenous methylprednisolone 1000 mg daily for 3 days, followed by gradual tapering of intravenous prednisolone from 50 mg daily to 20 mg daily for about 10 days. The patient died 22 days later after the event onset.

Table S6. HER2 Biomarker Analyses.*

Subject ID	<i>HER2</i> mutation exon location	<i>HER2</i> mutation subtype	Amino acid change	<i>HER2</i> amplification (gene copy number)	HER2 expression IHC score	Confirmed best overall response
1	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	0	SD
2	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	PR
3	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.14)	N/A	PR
4	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	PR
5	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (1.73)	N/A	PR
6	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	3+	PR

7	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (3.73)	2+	SD
8	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	SD
9	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	SD
10	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	PR
11	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	PR
12	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (1.69)	N/A	SD
13	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	0	SD
14	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.29)	0	PR
15	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.70)	N/A	SD

16	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (1.97)	3+	PR
17	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.40)	N/A	PR
18	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	SD
19	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.00)	N/A	SD
20	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	1+	SD
21	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	3+	SD
22	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	N/A
23	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (1.67)	0	PR
24	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.15)	3+	PR

25	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	SD
26	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	PR
27	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.10)	N/A	PR
28	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	3+	PR
29	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	0	PR
30	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (1.99)	N/A	PR
31	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.31)	2+	PR
32	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (1.71)	1+	PR
33	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	SD

34	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	SD
35	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	SD
36	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.14)	2+	SD
37	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	PR
38	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	PR
39	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.12)	3+	SD
40	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.19)	2+	SD
41	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.42)	N/A	PR
42	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (1.99)	N/A	PR

43	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.74)	2+	PR
44	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	PR
45	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	SD
46	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	SD
47	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	PR
48	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	0	SD
49	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.35)	2+	PR
50	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	N/A	PR
51	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Posit (6.45)	2+	PR

52	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	PR
53	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	2+	CR
54	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (1.97)	N/A	PR
55	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.34)	2+	PR
56	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	Neg (2.03)	N/A	PR
57	20	INS	p.Tyr772_Ala775dup/p.Ala775_Gl y776insTyrValMetAla	N/A	0	PR
58	20	INS	p.Gly778_Pro780dup	Neg (2.17)	N/A	PR
59	20	INS	p.Gly778_Pro780dup	N/A	N/A	PR
60	20	INS	p.Gly778_Pro780dup	Neg (2.62)	N/A	PR
61	20	INS	p.Gly778_Pro780dup	Neg (1.98)	1+	SD
62	20	INS	p.Gly778_Pro780dup	N/A	N/A	SD
63	20	INS	p.Gly778_Pro780dup	N/A	0	PR

64	20	INS	p.Gly778_Pro780dup	Neg (1.74)	3+	PR
65	20	INS	p.Gly778_Pro780dup	N/A	3+	PR
66	20	INS	p.Gly778_Pro780dup	N/A	0	SD
67	20	INS	p.Gly778_Pro780dup	Neg (2.01)	1+	N/A
68	20	INS	p.Gly776delinsValCys	Neg (1.85)	N/A	PR
69	20	INS	p.Gly776delinsValCys	Neg (3.39)	N/A	SD
70	20	INS	p.Gly776delinsValCys	Neg (1.66)	N/A	SD
71	20	INS	p.Gly776delinsValCys	N/A	3+	SD
72	20	INS	p.Gly776delinsValCys	Neg (1.74)	N/A	N/A
73	20	INS	p.Gly776delinsValCys	Neg (2.13)	2+	PR
74	20	INS	p.Gly776delinsValCys	Neg (2.00)	N/A	SD
75	20	INS	p.Gly776delinsValCys	N/A	1+	PR
76	20	INS	p.Gly776delinsValCys	N/A	3+	PR
77	20	INS	p.Ala775_Gly776insThrValMetAl a	Neg (2.35)	2+	PR
78	20	INS	p.Gly778_Ser779insLeuProSer	N/A	1+	SD
79	20	SNV	p.Gly776Ser	Neg (1.83)	2+	SD
80	20	SNV	p.Val777Leu	N/A	N/A	SD

81	20	SNV	p.Val777Leu	N/A	N/A	PR
82	19	SNV	p.Leu755Ser	N/A	1+	PR
83	19	SNV	p.Leu755Pro	Neg (3.03)	3+	PR
84	19	SNV	p.Leu755Pro	N/A	2+	SD
85	19	SNV	p.Asp769His	Neg (2.08)	N/A	SD
86	8	SNV	p.Ser310Phe	Neg (2.05)	2+	PD
87	8	SNV	p.Ser310Phe	Neg (2.36)	2+	PD
88	8	SNV	p.Ser310Phe	Posit (9.00)	N/A	PR
89	8	SNV	p.Ser310Phe	Neg (2.22)	2+	N/A
90	8	SNV	p.Ser310Tyr	N/A	N/A	PD
91	8	SNV	p.Ser310Tyr	N/A	N/A	SD

* Based on exploratory post hoc analyses.

CR, complete response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry;

N/A, not available; Neg, negative; PD, progressive disease; Posit, positive; PR, partial response;

SD, stable disease; SNV, single nucleotide variation.